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(54) Title: COMBINATION THERAPY COMPRISING METFORMIN AND ANTICONVULSANT AGENTS

(57) Abstract: Combination therapy comprising metformin and anticonvulsant derivatives useful for the treatment of obesity and for promoting weight loss are disclosed.

COMBINATION THERAPY COMPRISING METFORMIN AND ANTICONVULSANT AGENTS

FIELD OF THE INVENTION

The present invention is directed to a method for promoting weight loss and / or treating obesity comprising combination therapy with a therapeutically effective amount of metformin and an anticonvulsant agent, preferably topiramate.

BACKGROUND OF THE INVENTION

Obesity is a state of excess adipose tissue mass. Although often viewed as equivalent to increased body weight, this need not be the case-lean but very muscular individuals may be overweight by arbitrary standards without having increased adiposity. Body weights are distributed continuously in populations, so that a medically meaningful distinction between lean and obese is somewhat arbitrary. Obesity is therefore more effectively defined by assessing its linkage to morbidity or mortality.

Although not a direct measure of adiposity, the most widely used method to gauge obesity is the *body mass index* (BMI), which is equal to weight/height^2 (in kg/m^2). Other approaches to quantifying obesity include anthropometry (skin-fold thickness), densitometry (underwater weighing), computed tomography (CT) or magnetic resonance imaging (MRI), and electrical impedance. Using data from the Metropolitan Life Tables, BMIs for the midpoint of all heights and frames among both men and women range from 19 to 26 kg/m^2; at a similar BMI, women have more body fat than men. Based on unequivocal data of substantial morbidity, a BMI of 30 is most commonly used as a threshold for obesity in both men and women. Large-scale epidemiologic studies suggest that all-cause, metabolic, and cardiovascular morbidity begin to rise (albeit at a slow rate) when BMIs are ≥25, suggesting that the cut-off for obesity should be lowered. Some authorities use the term overweight (rather than obese) to describe individuals with BMIs between 25 or 27 and 30. A BMI between 25 and 30 should be viewed as medically significant

and worthy of therapeutic intervention, especially in the presence of risk factors that are influenced by adiposity, such as hypertension and glucose intolerance.

Recent data from the National Health and Nutrition Examination Surveys (NHANES) show that the percent of the American adult population with obesity (BMI > 30) has increased from 14.5% (between 1976 and 1980) to 22.5% (between 1998 and 1994). As many as 50% of U.S. adults ≥20 years of age were overweight (defined as BMI > 25) between the years of 1998 and 1991. Because substantial health risks exist in many individuals with BMI between 25 and 30, the increasing prevalence of medically significant obesity raises great concern. Obesity is more common among women and in the poor; the prevalence in children is also rising at a worrisome rate.

Obesity has major adverse effects on health. Morbidly obese individuals (>200% ideal body weight) have as much as a twelvefold increase in mortality. Morality rates rise as obesity increases, particularly when obesity is associated with increased intraabdominal fat (see above). It is also apparent that the degree to which obesity affects particular organ systems is influenced by susceptibility genes that vary in the population.

Hyperinsulinemia and insulin resistance are pervasive features of obesity, increasing with weight gain and diminishing with weight loss. Further, obesity is a major risk factor for diabetes, and as many as 80% of patients with type 2 diabetes mellitus are obese. Weight loss, even of modest degree, is associated with increased insulin sensitivity and often improves glucose control in diabetes.

The Framingham Study revealed that obesity was an independent risk factor for the 26-year incidence of cardiovascular disease in men and women [including coronary disease, stroke, and congestive heart failure (CHF)]. The effect of obesity on cardiovascular mortality in women may be seen at BMIs as low as 25. Obesity, especially abdominal obesity, is associated with an atherogenic lipid profile, with increased low-density lipoprotein (LDL) cholesterol, very low density lipoprotein and triglyceride, and decreased high-density lipoprotein cholesterol. Obesity is also associated with hypertension.

Obesity-induced hypertension is associated with increased peripheral resistance and cardiac output, increased sympathetic nervous system tone, increased salt sensitivity, and insulin-mediated salt retention; it is often responsive to modest weight loss.

Obesity may be associated with a number of pulmonary abnormalities. These include reduced chest wall compliance, increased work of breathing, increased minute ventilation due to increased metabolic rate, and decreased total lung capacity and functional residual capacity. Severe obesity may be associated with obstructive sleep apnea and the "obesity hypoventilation syndrome". Sleep apnea can be obstructive (most common), central, or mixed. Weight loss (10 to 20 kg) can bring substantial improvement, as can major weight loss following gastric bypass or restrictive surgery. Continuous positive airway pressure has been used with some success.

Obesity is associated with enhanced biliary secretion of cholesterol, supersaturation of bile, and a higher incidence of gallstones, particularly cholesterol gallstones. A person 50% above ideal body weight has about a sixfold increased incidence of symptomatic gallstones. Paradoxically, fasting increases supersaturation of bile by decreasing the phospholipid component. Fasting-induced cholecystitis is a complication of extreme diets.

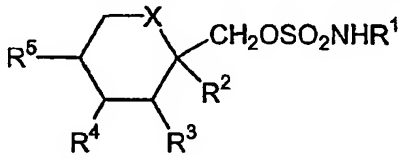
Obesity in males is associated with higher mortality from cancer of the colon, rectum, and prostate; obesity in females is associated with higher mortality from cancer of the gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries. Some of the latter may be due to increased rates of conversion of androstenedione to estrone in adipose tissue of obese individuals.

Obesity is associated with an increased risk of osteoarthritis, no doubt partly due to the trauma of added weight bearing. The prevalence of gout may also be increased. Among the skin problems associated with obesity is acanthosis nigricans, manifested by darkening and thickening of the skin folds on the neck, elbows, and dorsal interphalangeal spaces. Acanthosis reflects the severity of underlying insulin resistance and diminishes with weight loss. Friability of skin may be increased, especially in skin folds, enhancing the risk of fungal and yeast infections. Finally, venous stasis is increased in the obese.

(www.harrisons.accessmedicine.com Harrison's Online, Chapter 77: Obesity, Oct. 2004)

SUMMARY OF THE INVENTION

The present invention is directed to a method for treating obesity in mammals afflicted with such condition comprising administering to said mammal a therapeutically effective amount of a compound of the formula I:

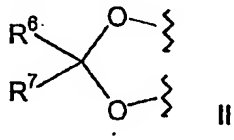


I

wherein X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula II:



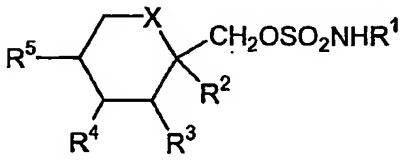
II

wherein

R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring;

and metformin.

The present invention is further directed to a method for promoting weight loss in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of the formula I:

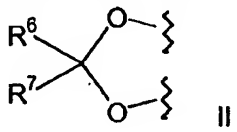


I

wherein X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula II:



II

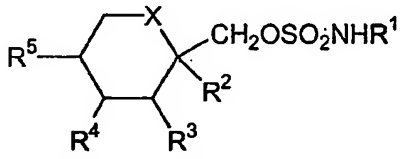
wherein

R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring;

and metformin.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is directed to a method for promoting weight loss and / or treating obesity comprising combination therapy with a therapeutically effective amount of metformin and an anticonvulsant agent, a compound of formula I



I

wherein R^1, R^2, R^3, R^4 and R^5 are as herein defined.

In an embodiment of the present invention, the mammals are preferably humans.

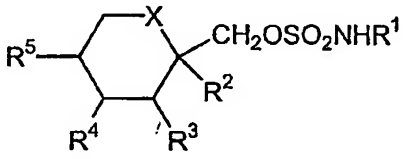
In an embodiment of the present invention, the compound of formula I is topiramate.

In an embodiment of the present invention, the compound of formula I is administered in an amount in the range of from about 25 to 600 mg. In another embodiment of the present invention, the compound of formula I is administered in an amount in the range of from about 50 to 200 mg once or twice daily.

In an embodiment of the present invention, the metformin is administered in an amount in the range of from about 500 to about 2500 mg daily. In another embodiment of the present invention, the metformin is administered in an amount in the range of from about 1000 to about 2000 mg daily.

In an embodiment, the present invention to methods of treatment comprising combination therapy wherein the amount of topiramate is therapeutically effective and wherein the amount of metformin is therapeutically effective.

The sulfamates of the invention are of the following formula I:

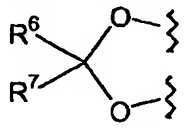


I

wherein X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula II:



II

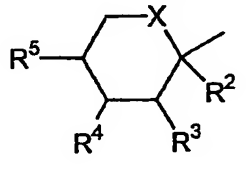
wherein R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R^2, R^3, R^4, R^5, R^6 and R^7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH_2, R^4 and R^5 may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R^4 and R^5 are defined by the alkatrienyl group =C-CH=CH-CH=.

A particular group of compounds of formula I is that wherein X is oxygen and both R^2 and R^3 and R^4 and R^5 together are methylenedioxy groups of the formula II, wherein R^6 and R^7 are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R^6 and R^7 are both alkyl such as methyl. A second group of compounds is that wherein X is CH_2 and R^4 and R^5 are joined to form a benzene ring. A third group of compounds of formula I is that wherein both R^2 and R^3 are hydrogen.

The compounds of formula I may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR^1$ in the presence of a base such as potassium *t*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF, or dimethylformamide wherein R is a moiety of the following formula (III):



(III)

(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as

triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl.

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R^1NH^2 at a temperature of abut 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula I. The reaction conditions for (b) are also described by T. Tsuchiya et al. in *Tetrahedron Lett.*, **1978**, 3365.

(c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula RCH_2OSO2N_3 as described by M. Hedayatullah in *Tetrahedron Lett.* **1975**, 2455. The azidosulfate is then reduced to a compound of formula I wherein R^1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R^2 and R^3 and R^4 and R^5 are identical and are of the formula II may be obtained by the method of R. F. Brady in *Carbohydr. Res.* **1970**, *14*, 35 or by reaction of the trimethylsilyl enol ether of a R^6COR^7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al. in *J. Org. Chem.* **1973**, *38*, 3935.

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH_2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium

borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I may also be made by the process disclosed US Patents: No.4,513,006, No.5,242,942, and No.5,384,327, which are incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments; i.e., below and above the plane of the drawing, of R^2, R^3, R^4 and R^5 on the 6-membered ring. Preferably, the oxygen of the methylenedioxy group II are attached on the same side of the 6-membered ring.

Metformin, also known as N,N-dimethylimidodicarbonimidic diamide, is an agent useful in the treatment of type II diabetes. Metformin is typically administered in the form of its hydrochloride salt and is currently available in the United States in Extended-Release Tablets.

Metformin is a biguanide oral antidiabetic agent that can be used in monotherapy or in combination with other classes of antidiabetic agents to lower blood glucose with additional therapeutic benefits, many believed to be related to a reduction in insulin resistance. Metformin, unlike many antidiabetic agents, does not cause weight gain and may lead to a small sustained reduction in weight. This is believed to be secondary to a decrease in energy intake. For this reason, metformin is often the agent of choice in overweight and obese subjects with type 2 diabetes.

As used herein, unless otherwise noted, the term **"therapeutically effective amount"**, means that amount of active compounds or pharmaceutical agents that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Wherein the present invention is directed to the administration of a combination of one or more anticonvulsant derivatives and metformin, **"therapeutically effective amount"** shall mean that amount of the combination of agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of combination therapy comprising administration of a compound of formula I and metformin would be the amount of the compound of formula I and the amount metformin that when taken together or sequentially have a combined effect that is therapeutically effective. Further, it will be recognized by one skilled in the art that in the case of combination therapy with a therapeutically effective amount, as in the example above, the amount of the compound of formula I and/or the amount of metformin individually may or may not be therapeutically effective.

Wherein the present invention is directed to the administration of a combination, the compounds may be co-administered by any suitable means, simultaneously, sequentially or in a single pharmaceutical composition. Where the compounds are administered separately, the number of dosages of each compound given per day, may not necessarily be the same, e.g. where one compound may have a greater duration of activity, and will therefore, be administered less frequently.

The compound(s) of formula I and metformin may be administered via the same or different routes of administration. The compound(s) of formula I and metformin may be administered via the same or different routes of administration. Suitable examples of methods of administration are orally, intravenous (iv), intramuscular (im), and subcutaneous (sc). Compounds may also be administrated directly to the nervous system including, but not limited to the intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal and/or peri-spinal routes of administration by delivery via intracranial or intravertebral needles and/or catheters with or without pump devices. The compound(s) of formula I and metformin may be administered

according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, time of administration and concomitant diseases, will result in the need to adjust dosages.

As used herein, the term **"composition"** is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula I are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., i.v. sterile injectable formulations will be prepared using appropriate solubilizing agents. A unit dose would contain about 15 to 200 mg of the active ingredient. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain some or all of the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The ability of the compounds of formula I administered in combination with metformin to treat obesity and/or to promote weight loss is based on the following clinical trial results.

Example 1

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of the Efficacy and Safety of Topiramate in the Treatment of Obese Type 2 Diabetic Subjects Treated With Metformin

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group study that evaluated 2 oral dosages of topiramate (96 mg/day and 192 mg/day) versus placebo in the treatment of obese type 2 diabetic subjects. Men and women between 18 to 75 years of age inclusive, with a body mass index (BMI) ≥27 kg/m^2 and <50 kg/m^2 and a history of type 2 diabetes mellitus treated with a stable dose of metformin monotherapy, HbA_{1c} <11%, and fasting plasma glucose (FPG) ≥7 mmol/L (126 mg/dL) and <13.1 mmol/L (240 mg/dL) were eligible for enrollment in the study. Subjects must have been taking metformin monotherapy for at least 4 months and have had a stable dose, not to exceed 2.1 g per day, for at least 2 months prior to enrollment. Subjects may have had an established diagnosis of controlled hypertension or dyslipidemia, with their antihypertensive and hypolipidemic medication stable for at least 2 months prior to enrollment.

Throughout the study, non-pharmacologic therapy, which consisted of an individual diet, a behavioral modification program, and a physical activity program, was provided to each subject. The energy level of the prescribed diet was 600 kcal (2500 kJ) less than the individual subject's calculated total energy expenditure. Non-pharmacologic therapy began at enrollment and continued through to Week 66, with assessments and advice concerning diet, exercise, and behavior at each visit.

The study consisted of 4 phases:

(a) ***6 week Run-In Phase*** during which subjects received single-blind placebo-treatment and began non-pharmacologic therapy. Eligibility was confirmed during the run-in phase and subjects who met study inclusion criteria and were deemed compliant with run-in placebo medication and non-

pharmacologic therapy and did not lose ≥6% of their enrollment body weight were to be randomized into 1 of the 3 treatment arms;

(b) ***8 week Titration Phase*** during which study medication was initiated at a dosage of 16 mg topiramate or placebo once daily in the evening. This was increased to 32 mg/day in Week 2 (16 mg b.i.d.) and by weekly increments of 32 mg/day. The dosage was increased (titrated) until the assigned (target) daily dosage or the maximum tolerated dosage, if less, was achieved;

(c) ***52 week Maintenance Phase*** during which subjects continued to receive placebo or topiramate at their assigned dosage or their maximum tolerated dosage for a period of 1 year;

(d) ***6 week Follow-Up Phase*** during which the subjects' dosage of study medication was decreased (tapered) by approximately 50% per week over a 2 week period and then was discontinued. A final visit was conducted 4 weeks after discontinuation of study treatment.

Efficacy was evaluated on the basis of data regarding body weight, HbA_{1c}, BMI, FPG, waist and hip circumference and waist/hip ratio, fasting lipid profile, fasting insulin, C-peptide, uric acid, urinary albumin excretion, blood pressure, and health-related quality of life (HRQOL) assessments. In addition, plasma topiramate and trough metformin plasma concentrations were measured for pharmacokinetic and pharmacokinetic/pharmacodynamic evaluations.

The following analysis populations were defined prior to unblinding:

(1) The **Intent-to-treat (ITT)** population for efficacy analysis included all randomized subjects who received at least 1 dose of study medication and had at least 1 on-treatment primary or secondary efficacy evaluation.

(2) The **Modified Intent-to-treat (MITT)** population was the primary population for efficacy analysis and consisted of all randomized subjects who received at least 1 dose of study medication and had at least 1 on-treatment primary or secondary efficacy evaluation AND who had the opportunity to complete at least 24 weeks of double-blind (8-week titration and 16-week

maintenance) treatment before announcement of early termination of the study.

(3) The **Safety population** was the primary population for safety analysis and included all randomized subjects who received at least 1 dose of study drug and for whom any safety information after the beginning of treatment was available.

The planned sample size for the study was 540 subjects (180 subjects per treatment group). This sample size was planned based on the condition that the study would be declared positive if there was a statistically significant positive effect on either of the 2 primary endpoints, and was the maximum of the sample sizes computed for the 2 primary efficacy variables with 95% power at a 0.025 two-sided significance level. The assumption was that it was important to detect a difference of 5% in percent weight change between active treatment and placebo groups after 1 year of therapy and that the standard deviation (SD) of the percent change was 11.0%. The assumption also was that it was important to detect a difference of 0.5% in mean HbA_{1c} change between active treatment and placebo groups after 1 year of therapy and that the standard deviation of the change was 1.2%. A power of 95% could be achieved for the HbA_{1c} analysis and a power of 98% could be achieved for the percent weight change analysis, each with a 2-sided significance level of 0.025.

Six hundred forty-six (646, 89%) of the 727 subjects enrolled in the study were randomly assigned to study treatment. Subjects were randomly assigned to receive placebo (N=210), topiramate 96 mg/day (N=221), or topiramate 192 mg/day (N=215) at 68 study sites. Two subjects erroneously received randomization numbers even though they did not complete the placebo run-in phase. Therefore, 644 subjects entered the double-blind phase of the study.

The Intent-to-treat population included 637 subjects. The Modified Intent-to-treat population included 307 subjects. Of the 646 subjects randomly

assigned to trial treatment, 640 (99%) subjects comprised the Safety population.

There were 83 (11%) of 727 subjects who discontinued from the study during the placebo run-in phase due to reasons including failure to meet study inclusion/exclusion criteria, subject choice, adverse events, lost to follow-up, and other reasons. Two subjects erroneously received randomization numbers even though they did not complete the placebo run-in phase. There were 644 (89%) subjects who continued in the study and were randomly assigned to receive placebo or topiramate.

Seventy-five (12%) subjects in the Safety population completed all study visits and 1 (<1%) subject completed the study by achieving maximum weight loss or decrease in HbA_{1c}. There were 186 (89%) of 208 subjects in the placebo group, 192 (88%) of 219 subjects in the 96 mg/day group, and 187 (88%) of 213 subjects in the topiramate 192 mg/day group who discontinued from the trial during the double-blind treatment phase. The percentage of subjects who were withdrawn from the study due to premature termination of the trial by the Sponsor was 64%, 64%, and 57% of subjects in the placebo, 96 mg/day, and 192 mg/day topiramate groups, respectively. Subjects receiving topiramate were more likely to discontinue due to adverse events than were subjects receiving placebo. Additional reasons for discontinuation were subject choice (7% placebo-treated subjects vs. 5% topiramate-treated subjects), lack of efficacy (5% vs. 2%), and lost to follow-up (1% vs. 2%).

Median by-subject average dosages were 87.8 mg/day in the topiramate 96 mg/day group and 160.5 mg/day in the topiramate 192 mg/day group across the titration and maintenance periods. The median average dosages during the maintenance period approached the target daily dosages (95.5 mg/day in the 96 mg/day group and 190.4 mg/day in the 192 mg/day group).

The planned duration of the treatment period, including the titration phase and the maintenance phase as stated in the protocol, was 60 weeks (420 days), followed by a 2-week tapering period. The median duration of

therapy, including the tapering period, was 196 days for the placebo group, 202 days for the topiramate 96 mg/day group, and 206 days for the topiramate 192 mg/day group.

Results

The primary efficacy variables in the study were mean percent change in weight and mean absolute change in HbA_{1c} from randomization (baseline) to the Week 24 value. Due to the correlation between these 2 variables, the nominal significance level α^* for the primary efficacy analyses was adjusted from 0.05 to 0.035.

Mean Percent Change in Body Weight

For the MITT group, subjects in each of the 2 topiramate treatment groups experienced a statistically significantly greater mean percent reduction from baseline body weight compared to subjects in the placebo group ($p<0.001$). The mean percent weight loss was -1.7% in the placebo group, -4.5% in the topiramate 96 mg/day group, and -6.5% in the topiramate 192 mg/day group. Results for the ITT population were similar to those of the MITT population. Results for the MITT and ITT populations were as listed in Tables 1 and 2 below.

Table 1:

Mean Percent Change from Baseline Body Weight Value (MITT Population)

	Placebo (N=100)	TPM 96 mg/day (N=102)	TPM 192 mg/day (N=105)
N[a]	97	102	103
Baseline Mean (kg)	102.7	100.7	99.0
Week 24[b] LOCF Value Mean (kg)	101.0	96.4	92.6
Mean % Change (SD)	-1.69 (3.02)	-4.49 (3.74)	-6.54 (4.77)
P value[c]		<0.001	<0.001

[a] Only subjects with both baseline and post-baseline values are included.
[b] The last assessment during the period of up to 24 total weeks of study therapy (4 months of maintenance therapy).
[c] Adjusted p values vs. placebo from Dunnett and Tamhane step-down multiple testing procedure.

Table 2:

Mean Percent Change from Baseline Body Weight Value (ITT Population)

	Placebo (N=207)	TPM 96 mg/day (N=217)	TPM 192 mg/day (N=213)
N[a]	203	215	209
Baseline Mean (kg)	103.2	102.5	99.6
Final[b] LOCF Value Mean (kg)	102.0	98.0	94.0
Mean % Change (SD)	-1.20 (3.29)	-4.49 (3.90)	-5.78 (5.10)
p value[c]		<0.001	<0.001

[a] Only subjects with both baseline and post-baseline values are included.
[b] The last assessment during the period of up to 60 total weeks of study therapy (12 months of maintenance therapy).
[c] P values vs. placebo from contrast statements.

Mean Percent Change in Body Weight Over Time

In the MITT population, weight loss was gradual through the end of the treatment period (Week 60). At Week 4 and all assessment times after Week 4, the mean percent weight decrease in each of the 2 topiramate dosage groups was significantly greater than the mean percent weight decrease in the placebo group. In the topiramate groups, the rate of weight loss decreased at approximately Week 32, but appeared to be ongoing to Week 48. Results for the ITT population were similar to those of the MITT population. Results for the MITT and ITT populations were as listed in Tables 3 and 4 below.

Table 3:

Mean Percent Change from Baseline Body Weight Over Time (MITT Population)

Week	Placebo		TPM 96 mg/day		TPM 192 mg/day	
	N, Mean	% Change	N, Mean	% Change	N, Mean	% Change
4	93	-0.64	97	-1.40	99	-1.88
8	88	-1.13	94	-2.55	92	-3.60
12	85	-1.74	93	-3.64	90	-4.99
16	81	-1.67	86	-4.24	89	-6.10
20	82	-1.75	84	-4.74	82	-6.62
24	75	-1.89	85	-4.94	86	-7.43
28	76	-2.09	87	-5.49	81	-7.40
32	74	-2.07	81	-5.78	78	-7.87
36	69	-2.00	75	-5.92	79	-8.04
40	68	-1.70	73	-6.43	73	-8.13
44	59	-1.40	61	-6.62	58	-8.14
48	48	-1.98	48	-6.85	50	-8.46
52	33	-1.09	38	-6.74	37	-8.69
56	34	-1.54	36	-6.60	33	-8.23
60	23	-1.85	30	-6.67	26	-8.46

Table 4:

Mean Percent Change from Baseline Body Weight Over Time (ITT Population

Week	Placebo		TPM 96 mg/day		TPM 192 mg/day	
	N, Mean	% Change	N, Mean	% Change	N, Mean	% Change
4	195	-0.60	206	-1.54	200	-1.59
8	185	-0.88	201	-2.66	186	-3.14
12	179	-1.26	193	-3.47	179	-4.36
16	169	-1.34	182	-4.00	169	-5.28
20	160	-1.38	173	-4.27	157	-5.67
24	132	-1.41	143	-4.67	139	-6.53
28	101	-1.88	111	-5.28	107	-7.24
32	86	-2.19	89	-5.82	88	-8.10

36	69	-2.00	75	-5.92	79	-8.04
40	68	-1.70	73	-6.43	73	-8.13
44	59	-1.40	61	-6.62	58	-8.14
48	48	-1.98	48	-6.85	50	-8.46
52	33	-1.09	38	-6.74	37	-8.69
56	34	-1.54	36	-6.60	33	-8.23
60	23	-1.85	30	-6.67	26	-8.46

Body Weight Responders

For the MITT population, fourteen percent of subjects in the placebo group, 42% of subjects in the topiramate 96 mg/day group, and 53% of subjects in the topiramate 192 mg/day group lost at least 5% of their baseline body weight, i.e., were '5% body weight responders.' Two percent of subjects in the placebo group, 11% in the topiramate 96 mg/day group, and 27% in the topiramate 192 mg/day group lost at least 10% of their baseline body weight, i.e., were '10% body weight responders.' All differences between topiramate and placebo were statistically significant ($p \leq 0.019$). Results for the ITT population were similar to those of the MITT population. Results for the MITT and ITT populations were as listed in Tables 5 and 6 below.

Table 5:

Number (%) of 5% and 10% Body Weight Responders (MITT Population)

Treatment	5% Responders[a]			10% Responders[b]		
	N	(%)	p-value[c]	N	(%)	p-value[c]
Placebo (N=100)	14	(14)		2	(2)	
Topiramate						
96 mg/day (N=102)	43	(42)	<0.001	11	(11)	0.019
192 mg/day (N=105)	56	(53)	<0.001	28	(27)	<0.001

[a] Subjects with 5% or greater body weight reduction from baseline at Week 24 LOCF.

[b] Subjects with 10% or greater body weight reduction from baseline at Week 24 LOCF.

[c] Topiramate vs. placebo (Cochran Mantel-Haenszel test stratified by site and sex).

Table 6:

Number (%) of 5% and 10% Body Weight Responders (ITT Population)

Treatment	5% Responders[a]			10% Responders[b]		
	N	(%)	p-value[c]	N	(%)	p-value[c]
Placebo (N=207)	26	(13)		3	(1)	
Topiramate						
96 mg/day (N=217)	90	(41)	<0.001	18	(8)	0.002
192 mg/day (N=213)	98	(46)	<0.001	42	(20)	<0.001

[a] Subjects with 5% or greater body weight reduction from baseline at the final value LOCF.

[b] Subjects with 10% or greater body weight reduction from baseline at the final value LOCF.

[c] Topiramate vs. placebo (Cochran Mantel-Haenszel test stratified by site and sex).

Summary and Conclusions

For the MITT population, the mean percent weight loss was 1.7% in the placebo group, 4.5% in the topiramate 96 mg/day group, and 6.5% in the topiramate 192 mg/day group. Both of the topiramate treatment groups were superior to placebo as indicated by statistically greater mean percent reductions from baseline body weight (p-values <0.001 for both groups).

Subjects who lost at least 5% or at least 10% of their weight from baseline to the Week 24 LOCF value were classified as 5% or 10% body weight responders. In the MITT population, 42% of subjects in the topiramate 96 mg/day group and 53% of subjects in the topiramate 192 mg/day group were 5% body weight responders. In contrast, 14% of subjects in the placebo group were 5% body weight responders. Similarly, a greater percentage of

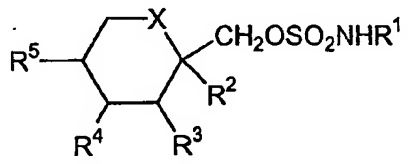
subjects were 10% body weight responders in the topiramate groups than in the placebo group. Eleven percent of subjects in the topiramate 96 mg/day group and 27% of subjects in the topiramate 192 mg/day group were 10% body weight responders compared with 2% of subjects in the placebo group.

Thus, in this study in obese type 2 diabetic subjects treated with a combination of metformin and both topiramate dosages – 96 and 192 mg/day – were superior to placebo as indicated by statistically greater mean reductions in percent body weight.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

What is claimed is:

1. A method for treating obesity in mammals afflicted with such condition comprising administering to said mammal a therapeutically effective amount of a compound of the formula I:

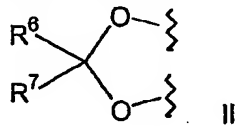


I

wherein X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula II:



II

wherein R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring;

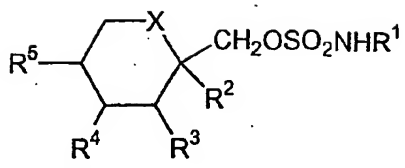
and metformin.

2. The method of claim 1 wherein the compound of formula I is topiramate.

3. The method of claim 1, wherein the therapeutically effective amount of the compound of formula I is from about 25 to 600 mg.

4. The method of claim 1, wherein the therapeutically effective amount of the compound of formula I is of from about 50 to 200 mg once or twice daily.

5. A method for promoting weight loss in a mammal in need thereof comprising administering to said mammal a therapeutically effective amount of a compound of the formula I:

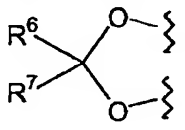


I

wherein X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula II:



II

wherein R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring;

and metformin.

6. The method of claim 1 wherein the compound of formula I is topiramate.

7. The method of claim 1, wherein the therapeutically effective amount of the compound of formula I is from about 25 to 600 mg.

8. The method of claim 1, wherein the therapeutically effective amount of the compound of formula I is of from about 50 to 200 mg once or twice daily.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/38508

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/70, 31/35, 31/255, 31/155
US CL : 514/23, 459, 517, 635, 909
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/23, 459, 517, 635, 909

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS-ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WERNEKE et al., "Option For Pharmacological Management of Obesity in Patients Treated with Atypical Antipsychotics", International Clinical Psychopharmacology, 2002, Vol. 17. No. 4, pages 145-160, see the entire document.	1-8
X	BAPTISTA et al., "Obesity and Related Metabolic Abnormalities During Antipsychotic Drug Administration: Mechanisms, Management and Research Perspectives", Pharmacopsychiatry 2002, Vol. 35, No. 6, pages 205-219, see the entire document.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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